IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

CANHAM et al. Atty. Ref.: ARC-2490-30

Serial No. 10/643,866 TC/A.U.: 1616

Filed: August 20, 2003 Examiner: Alstrum Acevedo

For: BIOMATERIAL

* * * * * * * * * * * *

September 18, 2007

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

SUBMISSION OF PRIORITY DOCUMENTS

It is respectfully requested that this application be given the benefit of the foreign filing date under the provisions of 35 U.S.C. §119 of the following, a certified copy of which is submitted herewith:

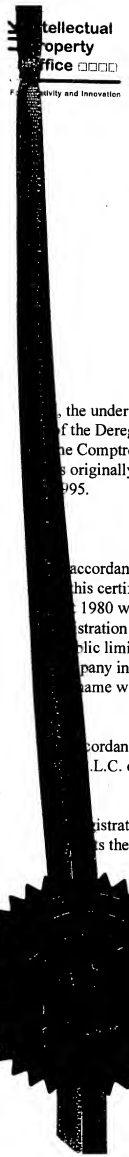
Application No.	Country of Origin	Filed
9515956.2	Great Britain	3 August 1995

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Arthur R. Crawford
Reg. No. 25,327

ARC:eaw
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100



Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) f the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of he Comptroller-General, hereby certify that annexed hereto is a true copy of the documents s originally filed in connection with patent application GB9515956.2 filed on 3 August 995.

accordance with the Patents (Companies Re-registration) Rules 1982, if a company named his certificate and any accompanying documents has re-registered under the Companies 1980 with the same name as that with which it was registered immediately before re-stration save for the substitution as, or inclusion as, the last part of the name of the words blic limited company" or their equivalents in Welsh, references to the name of the pany in this certificate and any accompanying documents shall be treated as references to ame with which it is so re-registered.

cordance with the rules, the words "public limited company" may be replaced by p.l.c., L.L.C. or PLC.

istration under the Companies Act does not constitute a new legal entity but merely s the company to certain additional company law rules.

Signed William Morell

Dated 13 September 2007

For official use

04AUG95 E135985-1 D02776
P01/7700 25.00

03 AUG 1995

Your reference
DERA/IPD01/P2292

9515956.2

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

2 Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

Warning
After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

BIOACTIVE MATERIAL

2 Applicant's details

☐ First or only applicant

2a If you are applying as a corporate body please give:

Corporate name
THE SECRETARY OF STATE FOR DEFENCE

Country *(and State of incorporation, if appropriate)*
UK

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c In all cases, please give the following details:

Address
DEFENCE EVALUATION AND RESEARCH AGENCY
FARNBOROUGH
HANTS

UK postcode GU14 6TD
(if applicable)

Country UNITED KINGDOM

ADP number
(if known) 5451000 3

RP

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

☐ **Second applicant (if any)**

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f In all cases, please give the following details:

Address

UK postcode
(if applicable)

Country

ADP number
(if known)

3
An address for service in the United Kingdom must be supplied.
Please mark correct box

3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ *go to 3b*

⬇ *Please give details below*

Agent's name
R.W.BECKHAM ET AL.
Agent's address
INTELLECTUAL PROPERTY DEPARTMENT
R69 BUILDING
DEFENCE RESEARCH AGENCY
FARNBOROUGH, HANTS.
Postcode GU14 6TD

Agent's ADP number 2576002/3

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

Daytime telephone number *(if available)*

ADP number
(if known)

4 Reference number

4 Agent's or applicant's reference number *(if applicable)* DERA/IPD01/P2292

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

⬇ *please give details below*

☐ number of earlier application or patent number

☐ filing date

(day month year)

☐ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

18(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6 If you are declaring priority from previous application(s), please give:

6 If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

Please mark correct box(es)

9

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

Please sign here ➡

A completed fee sheet should preferably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ ➡ ***A statement of inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)	3	Description	14
Abstract	1	Drawing(s)	6

8b Which of the following documents also accompanies the application?

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	1
Patents Form 9/77 - Preliminary Examination/Search	1
Patents Form 10/77 - Request for Substantive Examination	

9 Request

I/We request the grant of a patent on the basis of this application.

Signed (A. W. S. WILLIAMS) Date 02/08/1995 *(day month year)*

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

☐ ***The Comptroller***
The Patent Office
Cardiff Road
NEWPORT
Gwent
NP9 1RH

The Comptroller
The Patent Office
25 Southampton Buildings
London
WC2A 1AY

03 AUG 1995

For official use

THE PATENT OFFICE
03 AUG 1995
RECEIVED BY FAX

03 AUG 1995

9515956.2

Your reference

DERA/IPD01/P2292

Notes

Please type, or write in dark ink using CAPITAL letters.

No fee is required with this form.

Rule 15 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.
If you do not have enough space please use a separate sheet of paper.

When an application does not declare priority at all, or declares priority from an earlier UK application, sufficient additional copies of this form must be supplied to enable the Comptroller to send one to each inventor who is not an applicant.

The Patent Office

Statement of inventorship and of right to grant of a Patent

Form 7/77 **Patents Act 1977**

1 Application details

1a Please give the patent application number (if known):

1b Please give the full name(s) of the applicant(s):

THE SECRETARY OF STATE FOR DEFENCE

2 Title of invention

2 Please give the title of the invention:

BIOACTIVE MATERIAL

3 Derivation of right

3 Please state how the applicant(s) derive(s) the right to be granted a patent:

UNDER SECTION 39(1) OF THE PATENTS ACT 1977 BY VIRTUE OF THE INVENTOR'S EMPLOYMENT BY THE SECRETARY OF STATE FOR DEFENCE

4 Declaration

4 I believe the person(s) named overleaf (and on any supplementary copies of this form) to be the inventor(s) of the invention for which the patent application has been made. I consent to the disclosure of the details contained in this form to each inventor named.

Please sign here ➡

Signed (A.W. Sawyers)

Date 02/08/1995 *(day month year)*

Please turn over ⇨

Please put the full name(s) and address(es) of the inventors in the boxes below:

Please underline the surnames or family names.

LEIGH TREVOR CANHAM
DEFENCE RESEARCH AGENCY
ST ANDREWS ROAD
MALVERN
WORCS
WR14 3PS 6121813001

ADP number (if known):

ADP number (if known):

ADP number (if known):

Please give the names of any further inventors on the back of another form 7/77 and attach it to this form.

Reminder

Have you signed the declaration overleaf?

BIOACTIVE MATERIAL

The present invention relates to bioactive materials and more particularly bioactive silicon.

A "biomaterial" is a non-living material used in a medical device which is intended to interact with biological systems. Such materials may be relatively "bioinert", "bioactive" or "resorbable", depending on their biological response in vivo.

Bioactive materials are a class of materials each of which when in vivo elicits a specific biological response that results in the formation of a bond between living tissue and that material. Bioactive materials are also referred to as surface reactive biomaterials. Biomaterials may be defined as materials suitable for implantation into a living organism. L.L.Hench has reviewed biomaterials in a scientific paper published in Science, Volume 208, May 1980, pages 826-831. Biomaterials which are relatively inert may cause interfacial problems when implanted and so considerable research activity has been directed towards developing materials which are bioactive in order to improve the biomaterial-tissue interface.

Known bioactive materials include hydroxyapatite (HA), some glasses and some glass ceramics. Both bioactive glasses and bioactive glass ceramics form a biologically active layer of hydroxycarbonateapatite (HCA) when implanted. This layer is equivalent chemically and structurally to the mineral phase in bone and is responsible for the interfacial bonding between bone and the bioactive material. The properties of these bioactive materials are described by L.L.Hench in the Journal of the American Ceramic Society, Volume 74 Number 7, 1991, pages 1487-1510. The scientific literature on bioactive materials often uses the terms HA and HCA on an interchangeable basis. In this patent specification, the materials HA and HCA are collectively referred to as apatite.

Li et al. have reported the deposition of apatite on silica gel in the Journal of Biomedical Materials Research, Volume 28, 1994, pages 7-15. They suggest that a certain density of silanol (SiOH) groups is necessary to trigger the heterogeneous nucleation of hydroxyapatite. An apatite layer did not develop on the surface of a silica glass sample and this is attributed to the lower density of surface silanol groups compared with silica gel.

Thick films of apatite have previously been deposited on silicon single crystal wafers by placing the wafers in close proximity to a plate of apatite and wollastonite-containing glass dipped into a physiological solution at 36° C, as described by Wang et al. in the Journal of Materials Science: Materials In Medicine, Volume 6, 1995, pages 94-104. A physiological solution, also known as a simulated body fluid (SBF), is a solution containing ion concentrations similar to those found in the human body and is widely used to mimic the behaviour of the body in in vitro tests of bioactivity. Wang et al. reported the growth of apatite on (111) Si wafers but reported that "hardly any" apatite could be grown on (100) Si wafers. The silicon wafer itself is not bioactive. Wang et al. state that "Si does not play any special role in the growth of (the) apatite film except that Si atoms on the substrate can bond strongly with oxygen atoms in apatite nuclei to form interfaces with low energy". The presence of the apatite and wollastonite containing glass is required to induce the deposition of the apatite. Indeed, this so-called "biomimetic process" whereby a bioactive material is used to treat another material has been shown to induce apatite growth on a wide variety of bioinert materials, as reported by Y.Abe et al. in the Journal of Materials Science: Materials In Medicine, Volume 1, 1990, pages 233 to 238.

There is a long felt want for the ability to use silicon based integrated circuits within the human body both for diagnostic and therapeutic purposes. Silicon has been reported to exhibit a poor biocompatibility in blood (Kanda et al. in Electronics Letters, Volume 17, Number 16, 1981, pages 558 and 559), and in order to protect integrated circuits from damage in biological environments encapsulation by a suitable

material is required. Medical applications for silicon based sensors are described in a paper by Engels et al. in the Journal of Physics E: Sci. Instrum., Volume 16, 1983, pages 987 to 994.

The present invention provides bioactive silicon.

Bioactive silicon provides the advantage over other bioactive materials that it is compatible with silicon based integrated circuit technology. It has the advantage over non-bioactive silicon that it exhibits a greater degree of biocompatibility. In addition, bioactive silicon may be used for forming a bond to bone or vascular tissue of a living animal. Bioactive silicon may provide a material suitable for use as a packaging material in miniaturised packaging applications.

The bioactive nature of the silicon may be demonstrated by the immersion of the material in a simulated body fluid held at a physiological temperature, such immersion producing a mineral deposit on the bioactive silicon. The mineral deposit may be apatite. The apatite deposit may be continuous over an area greater than 100 μm^2. The bioactive silicon may be at least partially porous silicon. The porous silicon may have a porosity greater than 4% and less than 70%.

Bulk crystalline silicon can be rendered porous by partial electrochemical dissolution in hydrofluoric acid based solutions, as described in United States Patent No. 5,348,618. This etching process generates a silicon structure that retains the crystallinity and the crystallographic orientation of the original bulk material. The porous silicon thus formed is a form of crystalline silicon. At low levels of porosity, for example less than 20%, the electronic properties of the porous silicon resemble those of bulk crystalline silicon.

Porous silicon may be subdivided according to the nature of the porosity. Microporous silicon contains pores having a diameter less than 20 Å; mesoporous silicon contains pores having a diameter in the range 20 Å to 500 Å; and macroporous

silicon contains pores having a diameter greater than 500 Å. The bioactive silicon may comprise porous silicon which is either microporous or mesoporous.

Silicon has never been judged a promising biomaterial, in contrast with numerous metals, ceramics and polymers, and has never been judged capable of exhibiting bioactive behaviour. Indeed, no semiconductors have been reported to be bioactive. Silicon is at best reported to be relatively bioinert but generally exhibits poor biocompatibility. Despite the advances made in miniaturisation of integrated circuitry, silicon VLSI technology is still under development for invasive medical and biosensing applications, as described by K.D.Wise et al. in "VLSI in Medicine" edited by N.G.Einspruch et al., Academic Press, New York, 1989, Chapter 10 and M.Madou et al. in Appl. Biochem. Biotechn., Volume 41, 1993, pages 109-128.

In a further aspect, the invention provides a bioactive silicon structure.

In a still further aspect, the invention provides an electronic device for operation within a living animal body wherein the device includes bioactive silicon.

Bioactive silicon of the invention may be arranged as a protective covering for an electronic circuit as well as a means for attaching a device to bone or other tissue.

The electronic device may be a sensor device or a device for intelligent drug delivery or a prosthetic device.

In a still further aspect, the invention provides a method of making silicon bioactive wherein the method comprises making at least part of the silicon porous.

In order that the invention may be more fully understood, embodiments thereof will now be described, by way of example only, with reference to the accompanying drawings, in which:-

Figure 1 is a schematic sectional diagram of a bioactive silicon wafer;

Figure 2 is a representation of a scanning electron microscope (SEM) micrograph of an apatite deposit on a bulk silicon region adjacent a porous region of the Figure 1 wafer;

Figure 3 is a representation of an SEM micrograph of a cross-section of the Figure 2 silicon region;

Figure 4 is a representation of an SEM micrograph showing an apatite spherulite deposited on a porous silicon region of porosity 31%

Figure 5a is a representation of an SEM micrograph of an unanodised region of a silicon wafer anodised to produce a porosity of 48% after immersion in a simulated body fluid solution;

Figure 5b is a representation of an SEM micrograph of an anodised region of the Figure 5a wafer; and

Figure 6 is a schematic diagram of a biosensor incorporating bioactive silicon.

Referring to Figure 1 there is shown a section of a bioactive silicon wafer, indicated generally by 10. The silicon wafer 10 comprises a porous silicon region 20 and a non-porous bulk silicon region 22. The porous region 20 has a thickness d of 13.7 μm and an average porosity of 18%. The silicon wafer 10 has a diameter l of three inches or 75 mm. The porous region 20 has a surface area per unit mass of material of 67 m^2g^{-1}. This was measured using a BET gas analysis technique, as described in "Adsorption,

Surface Area and Porosity" by S.J.Gregg and K.S.W.Sing, 2nd edition, Academic Press, 1982.

The wafer 10 was fabricated by the anodisation of a heavily As doped Czochralski-grown (CZ) n-type (100) silicon wafer having an initial resistivity of 0.012 Ωcm. The anodisation was carried out in an electrochemical cell, as described in United States Patent No. 5,348,618, containing an electrolyte of 50 wt% aqueous HF. The wafer was anodised using an anodisation current density of 100 $mAcm^{-2}$ for one minute. The wafer was held in place in the electrochemical cell by a synthetic rubber washer around the outside of the wafer. Consequently, an outer ring of the wafer remained unanodised after the anodisation process. This outer unanodised ring is shown in Figure 1 as a non-porous bulk silicon region 22. The unanodised ring has a width s of 4 mm.

In order to determine the bioactivity of anodised wafers, cleaved wafer segments were placed in a simulated body fluid (SBF) solution for a period of time ranging from 2 hours to 6 weeks. The SBF solution was prepared by dissolving reagent grade salts in deionised water. The solution contained ion concentrations similar to those found in human blood plasma. The SBF solution ion concentrations and those of human blood plasma are shown at Table 1. The SBF solution was organically buffered at a pH of 7.30 ± 0.05, equivalent to the physiological pH, with trihydroxymethylaminomethane and hydrochloric acid. The porous wafers were stored in ambient air for at least several months prior to immersion in the SBF solution and were therefore hydrated porous silicon wafers. The porous silicon thus comprised a silicon skeleton coated in a thin native oxide, similar to that formed on bulk silicon as a result of storage in air.

Table 1

Ion	Concentration (mM)	
	Simulated Body Fluid	Human Plasma
Na^+	142.0	142.0
K^+	5.0	5.0
Mg^{2+}	1.5	1.5
Ca^{2+}	2.5	2.5
HCO_3^-	4.2	27.0
HPO_4^{2-}	1.0	1.0
Cl^-	147.8	103.0
SO_4^{2-}	0.5	0.5

Cleaved wafer segments having typical dimensions of 0.4 x 50 x 20 mm^3 were placed in 30 cm^3 capacity polyethylene bottles filled with the SBF solution and held at 37° ± 1° C by a calibrated water bath.

After a known period of time, the segments were removed from the SBF solution, rinsed in deionised water and allowed to dry in ambient air prior to characterisation. The SBF treated segments were examined using scanning electron microscopy (SEM) and x-ray microanalysis (EDX) on a JEOL 6400F microscope. Secondary ion mass spectrometry was carried out using a Cameca 4F instrument and infrared spectroscopy was performed using a Biorad FTS-40 spectrometer.

After periods of immersion in the SBF solution of 2, 4, and 17 hours, there were negligible apatite deposits on both the porous silicon region 20 and the non-porous bulk silicon region 22.

Referring to Figure 2 there is shown a reproduction of an SEM micrograph indicated generally by 50. The micrograph 50 is an image of part of the region 22 after the wafer 10 had been placed in the SBF solution for a period of 6 days. A scale bar 52 indicates a dimension of 2 μm. The micrograph 50 shows a continuous layer of apatite

spherulites 54 covering the surface of the region 22. The apatite spherulites had nucleated at a sufficiently high density to create a relatively smooth film in which boundaries between spherulites such as boundary 56 are indistinct. The film was continuous over an area of at least 100 μm^2.

Referring to Figure 3 there is shown a reproduction of an SEM micrograph, indicated generally by 100, of a cross-section of the wafer 10 in the region 22 after the wafer had been immersed in the SBF solution for 6 days. A scale bar 102 indicates a dimension of 1.0 μm. The micrograph 100 indicates three distinct regions, indicated by the letters A, B, and C. EDX analysis confirmed that region A is silicon, corresponding to the original material of the non-porous bulk silicon region 22. Region B exhibited both silicon and oxygen peaks under EDX analysis, indicating that region B comprises silicon oxide. Region C exhibited calcium, phosphorus and oxygen peaks under EDX analysis, consistent with this region comprising spherulites of apatite. The combined SEM and EDX analysis demonstrates that a porous silicon oxide layer (region B) has formed on the bulk silicon (region A), thereby enabling nucleation and coverage with apatite (region C).

SEM analysis of the wafer 10 in the area of the porous silicon region 20 after 6 days immersion in the SBF solution indicated a much lower level of apatite coverage compared with the region 22. The porous silicon region 20 contains a high level of mesoporosity. After 10 days immersion in the SBF solution in which significant layer erosion of the porous silicon had occurred, macropores were visible under SEM analysis in the region 20. The combined SEM and EDX analysis demonstrates that, in contrast to the bulk silicon region 22, apatite nucleation can occur directly on the porous silicon region 20 and does not require the formation of an intermediate porous silicon oxide layer. The intentional introduction of very large (greater than 100 μm diameter) macropores may be advantageous in that it may enable vascular tissue to grow within the structure of the porous silicon.

The formation of apatite deposits has also been observed on wafers having porous silicon porosities other than 18%. A microporous wafer having a porous silicon region with a porosity of 31% was fabricated from a 0.03 Ωcm heavily boron doped p-type CZ silicon wafer by anodisation at an anodisation current density of 100 $mAcm^{-2}$ for one minute in 50 wt% HF. The resulting porous silicon region had a thickness of 9.4 μm and a surface area per unit mass of 250 m^2g^{-1}. The porous silicon wafer was heavily aged prior to immersion in the SBF solution.

Figure 4 shows a representation of an SEM micrograph, indicated generally by 150, of the surface of the 31% porosity porous silicon layer after a segment of the wafer had been immersed in 30 cm^3 of the SBF solution for 7 days. The micrograph 150 shows spherulites such as a spherulite 152 of apatite on the surface (154) of the porous silicon.

Microporous wafers having a porous silicon region of a porosity of 48% were fabricated by anodising a lightly boron doped p-type silicon wafer having a resistivity of 30 Ωcm in 50 wt% HF at an anodisation current density of 20 $mAcm^{-2}$ for five minutes. The resulting porous silicon region had a thickness of 6.65 μm and a surface area per unit mass of approximately 800 m^2g^{-1}. The porous silicon wafer segment was heavily aged prior to immersion in a 150 cm^3 polyethylene bottle filled with the SBF solution.

Figure 5a shows a representation of a SEM micrograph, indicated generally by 200, of an apatite deposit 202 on an unanodised region of the 48% porosity wafer after a four week immersion period. Figure 5b shows a representation of a SEM micrograph, indicated generally by 250 of an apatite spherulite 252 deposited on the 48% porosity porous region. The spherulite 252 exhibits a morphology having a columnar structure characteristic of apatite growth on bioactive ceramics as described by P.Li et al. in Journal of Biomedical Materials Research, Volume 28, pages 7-15, 1994. Apatite spherulites having a similar morphology were observed on the unanodised region of the wafer. Cross-sectional EDX spectra of the 48% porosity wafer after immersion in

the SBF solution taken across the unanodised region indicated that spherulites contained calcium, phosphorus and oxygen, consistent with apatite. Away from the spherulites, an interfacial layer having a thickness of only 150 nm comprising predominantly silicon and oxygen was observed. Fourier transform infrared spectroscopy confirms the presence of apatite in both the porous and non-porous regions. Both the P-O bending vibrational modes of PO_4 tetrahedra at wavenumbers of around 600 cm^{-1} and a broad band around 1400 cm^{-1}, attributed to vibrational modes of carbonate groups, were observed.

Some forms of porous silicon are known to be photoluminescent. The observation of red or orange photoluminescence from porous silicon generally indicates the presence of quantum wires or quantum dots of silicon material. Prior to immersion in the SBF solution, the heavily aged 48% porosity wafer exhibited photoluminescence, indicating that despite being hydrated by exposure to ambient air, the porous silicon region maintains a high concentration of quantum wires or dots. The luminescent property was preserved both during and after immersion in the SBF solution. This shows that apatite may be deposited on porous silicon such that the luminescent properties are preserved. Preservation of the luminescent properties after growth of an apatite layer may be a useful property for the development of an electro-optical biosensor.

A wholly mesoporous luminescent porous silicon wafer having a 1 μm thick porous region with a porosity of 70% and a surface area per unit mass of 640 m^2g^{-1} was placed in the SBF solution. After approximately one day the porous region had been completely removed by dissolution in the SBF solution and the wafer was no longer luminescent. No apatite deposits were observed on either the porous silicon region or the non-porous region. It is thought that the mesoporous silicon is wetted more efficiently by the SBF solution and hence the rate of dissolution is higher for mesoporous silicon than microporous silicon. The mesoporous silicon thus shows resorbable biomaterial characteristics. It might be possible to construct a bioactive silicon structure having a limited area of mesoporous silicon to act as a source of

soluble silicon. This could produce a locally saturated silicon solution and hence the promotion of apatite deposition.

A macroporous silicon wafer having a porous region of 4% porosity and a thickness of 38 μm behaved like a bulk, unanodised silicon wafer in as much as it did not exhibit growth of an apatite deposit when immersed in the SBF solution for four weeks. In addition, no apatite growth has been observed on a porous silicon region having a porosity of 80% and a thickness of 50 μm which retains its luminescent properties after two weeks immersion in the SBF solution.

As a further control, a cleaved non-porous silicon wafer segment of similar dimensions to the porous silicon wafer segments was placed in 30 cm^3 of the SBF solution. An extremely low density of micron size deposits, less than 5000/cm^2 was observed after immersion in the SBF solution for five weeks. These deposits were possibly located at surface defects of the silicon wafer. Bulk, non-porous silicon is therefore not bioactive since the rate of growth of apatite deposits is too low for a bond to be formed with living tissue.

These experiments thus indicate that by appropriate control of pore size and porosity, silicon structures can cover virtually the entire bioactivity spectrum. Bulk and purely macroporous silicon are relatively bioinert; high porosity mesoporous silicon is resorbable and microporous silicon of moderate porosity is bioactive.

It is known that changes in chemical composition of biomaterials can also affect whether they are bioinert, resorbable or bioactive. The above experiments were carried out on porous silicon wafers which had not been intentionally doped with any specific elements other than the impurity doping for controlling the semiconductor properties of the silicon.

The elution of calcium from bioactive glass containing SiO_2, Na_2O, CaO and P_2O_5 is believed to significantly assist apatite growth by promoting local supersaturation.

Calcium has been impregnated into a freshly etched layer of microporous silicon of 55% porosity and having a thickness of 1.2 μm formed in a lightly doped p-type (30 Ωcm) CZ silicon wafer by anodisation at 20 $mAcm^{-2}$ for one minute in 40% aqueous HF. The calcium impregnation was achieved through mild oxidation by storage in a solution containing 5 g of $CaCl.2H_2O$ in 125 cm^3 pure ethanol for 16 hours. The impregnation of the porous silicon with calcium, sodium or phosphorus or a combination of these species may promote apatite formation on silicon.

The presence of the silicon oxide layer underneath the apatite deposit at the non-porous region adjacent the porous silicon region of the anodised wafers after immersion in the SBF solution indicates that the dissolution of silicon from the porous silicon region may be an important factor for the bioactivity of the porous silicon. The dissolution of the silicon may form a local supersaturated solution which results in the deposition of a porous silicon oxide layer. Apatite is then deposited on the porous silicon oxide. This suggests that a variety of non-porous crystalline, polycrystalline or amorphous silicon based structures containing impregnated calcium and having a higher solubility than normal bulk crystalline silicon in the SBF solution may be bioactive. To significantly assist apatite growth, the level of calcium impregnation needs to be much higher than previously reported calcium doped silicon, though the crystallinity of the silicon need not necessarily be preserved.

Calcium is generally regarded as an unattractive dopant for silicon and consequently there have been few studies of calcium doped silicon. Sigmund in the Journal of the Electrochemical Society, Volume 129, 1982, pages 2809 to 2812, reports that the maximum equilibrium solubility of calcium in monocrystalline silicon is 6.0×10^{18} cm^{-3}. At this concentration, calcium is unlikely to have any significant effect upon apatite growth. Supersaturated levels of calcium are needed with concentrations in excess of 10^{21} cm^{-3} (2 at%). Such very high concentrations may be achieved by:

(a) solution doping of porous silicon as previously described;

(b) ion implantation of porous silicon or bulk silicon with calcium ions; or

(c) epitaxial deposition of calcium or calcium compounds followed by thermal treatments.

Referring to Figure 6 there is shown a schematic diagram of a generalised sensor, indicated generally by 300, for medical applications incorporating bioactive silicon. The sensor 300 comprises two silicon wafer segments 302 and 304. The segment 302 incorporates CMOS circuitry 306 and a sensing element 308 linked to the circuitry 306. The sensing element 308 may be an oxygen sensor, for instance a Clark cell. The CMOS circuitry is powered by a miniaturised battery (not shown) and signals are produced for external monitoring using standard telemetry techniques.

The wafer segment 304 is a micromachined top cover for the segment 302. The segment 304 has two major cavities 310 and 312 machined into it. The cavity 310 has a dome shape. When the segments 302 and 304 are joined together, the cavity 310 is above the CMOS circuitry 306. The cavity 312 is circular in cross-section and extends through the segment 304 to allow the sensing element 308 to monitor the environment surrounding the sensor. The cavity 312 is covered by a permeable membrane 314. In addition to the major cavities 310 and 312, minor cavities, such as cavities 316, are distributed over a top surface 322 of the segment 304. The minor cavities are frusto-conical in shape, with the diameter of its cross-section increasing into the segment. The minor cavities are present to enable the growth of vascular tissue or bone for biological fixation. The cavities 310, 312, and 316are formed by standard etching techniques, for example ion-beam milling and reactive ion etching through a photoresist mask. At least part of the outer surfaces of the segments 302 and 304 are anodised to form a porous silicon region in order to promote the deposition of apatite and the bonding of the sensor with the tissue. In Figure 6, the porous silicon is indicated by rings 330 on the top surface of the segment 304 and grooves 332 in the other surfaces. Although Figure 6 indicates that the outer surfaces of the segments 302 and 304 are covered entirely by porous silicon, it may be sufficient for only the surface 322 and a bottom surface 334 of the segment 302 to incorporate porous silicon. Such an arrangement would be simpler to fabricate. The segments 302 and 304 are bonded

together using techniques developed for silicon on insulator technologies. Whilst an anodisation technique has been described for the production of the porous silicon, stain etching techniques are also known for the production of porous silicon. Such techniques may be advantageous for producing porous silicon surfaces on complex shaped structures.

In addition to sensors, bioactive silicon might find applications in electronic prosthetic devices, for example replacement eyes. Other electronic devices which may incorporate bioactive silicon might include intelligent drug delivery systems.

Whilst the results of in vitro experiments have been described, no in vivo experiments have been described. However, the in vitro experiments are designed to mimic the environment within a human body. From the results of the in vitro experiments it may be concluded that those silicon wafers which produced significant deposits of apatite in the SBF solution would also exhibit bioactive behaviour in vivo.

CLAIMS

1. Bioactive silicon.

2. Bioactive silicon according to Claim 1 wherein when immersed in a simulated body fluid solution held at a physiological temperature the silicon induces the deposition of a mineral deposit thereon.

3. Bioactive silicon according to Claim 2 wherein the mineral deposit is apatite.

4. Bioactive silicon according to Claim 3 wherein the apatite is continuous over at least an area of 100 μm^2.

5. Bioactive silicon according to Claim 1 wherein the silicon is at least partially porous with a porosity greater than 4% and less than 70%.

6. Bioactive silicon according to Claim 5 wherein the porous silicon is microporous.

7. Bioactive silicon according to Claim 5 wherein the porous silicon is mesoporous.

8. Bioactive silicon according to Claim 1 or Claim 5 wherein the silicon is impregnated with at least one species taken from a list of calcium, sodium and phosphorus.

9. Bioactive silicon according to Claim 5 wherein the porous silicon is visibly luminescent.

10. A bioactive silicon structure.

11. A bioactive silicon structure according to Claim 10 wherein the structure comprises a porous silicon region having a porosity greater than 4% and less than 70%.

12. A bioactive silicon structure according to Claim 11 wherein the porous silicon is microporous.

13. A bioactive silicon structure according to Claim 11 wherein the porous silicon is mesoporous.

14. A bioactive silicon structure according to Claim 11 wherein the structure also includes macropores.

15. A bioactive silicon structure according to Claim 10 or Claim 11 wherein the silicon is impregnated with at least one species taken from a list of calcium, sodium and phosphorus.

16. A bioactive silicon structure according to Claim 10 wherein the structure includes resorbable silicon material.

17. A bioactive silicon structure according to Claim 15 wherein the porous silicon is impregnated with calcium at a concentration greater than 10^{21} cm^{-3}.

18. An electronic device for operation within a living human or animal body wherein the device includes bioactive silicon.

19. An electronic device according to Claim 18 wherein the bioactive silicon comprises at least partially porous silicon having a porosity greater than 4% and less than 70%.

20. An electronic device according to Claim 19 wherein the porous silicon contains macropores for enhancing vascular tissue ingrowth.

21. An electronic device according to Claim 19 wherein the porous silicon extends at least partially over an outer surface of the device.

22. An electronic device according to any one of Claims 18 to 21 wherein the device is a sensor device.

23. A method of making silicon bioactive wherein the method comprises making at least part of the silicon porous.

24. A method according to Claim 23 wherein the method includes the impregnation of calcium.

25. The use of bioactive silicon for the construction of a device for use in a living human or animal body.

26. Bioactive silicon for use in a method of treatment of the human or animal body.

27. Bioactive silicon incorporated in a device suitable for use in a living human or animal body.

ABSTRACT

Bioactive material may be fabricated by anodising a silicon wafer to produce a wafer (10) having a porous silicon region (20). In vitro experiments have shown that certain types of porous silicon cause the deposition of apatite deposits both on the porous silicon (20) and neighbouring areas of bulk silicon (22) when immersed in a simulated body fluid solution.

Figure 1 should accompany the abstract.

Fig 2

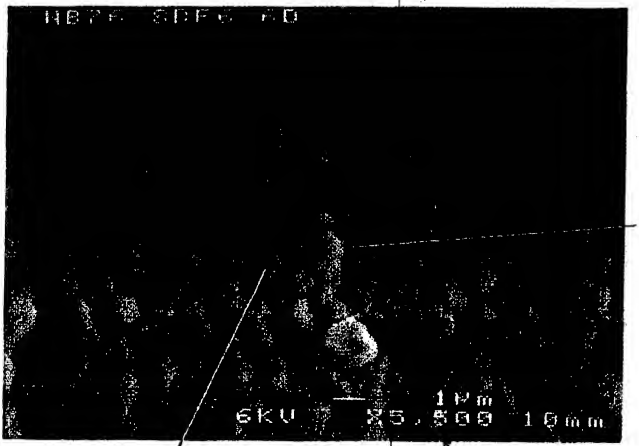


Fig 1

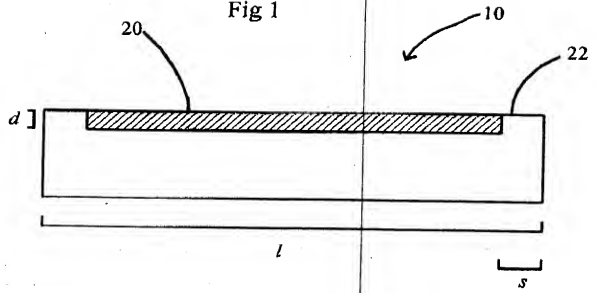


Fig 3

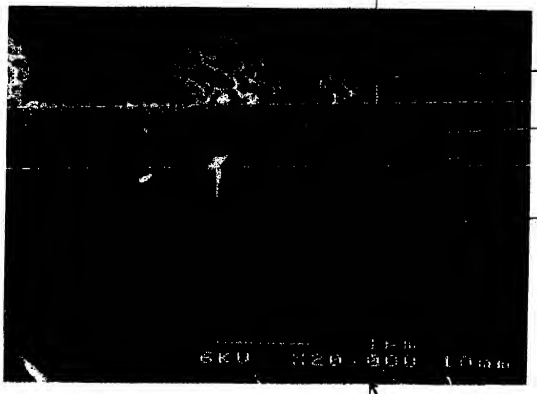


Fig 4

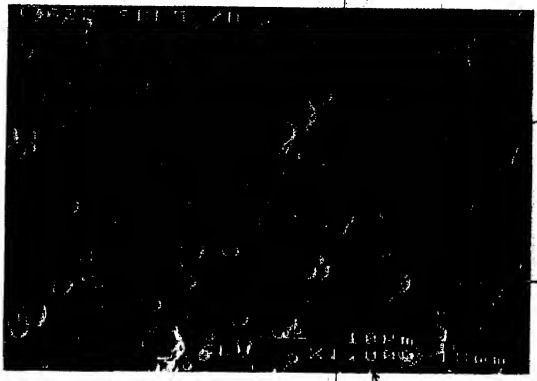


Fig 5a

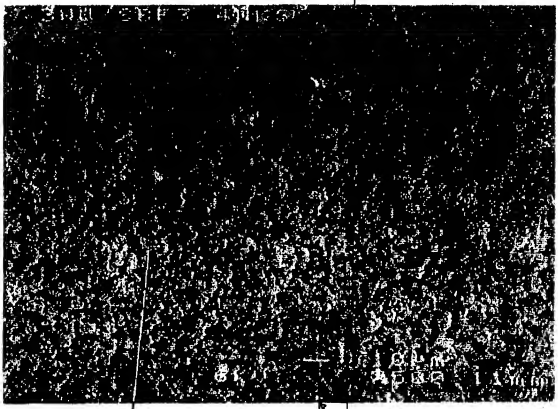
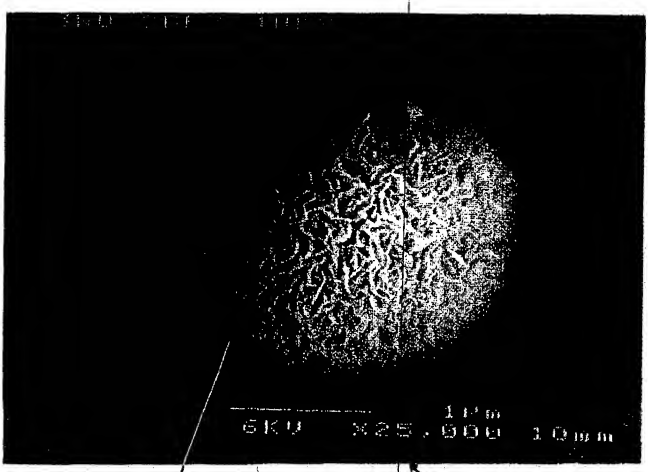


Fig 5b



252

250

Fig 6